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08/573,569	12/14/95	MAASSAB	H 203442025701

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EXAMINER	
GOTTLIEB,P	
ART UNIT	PAPER NUMBER
1813	

DATE MAILED: 03/06/97

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/573,569	Maassab H
Examiner	**Group Art Unit**
Gottlieb	1813

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 4, 5, 7, 8, 12, 19, 20, 22, 23, and 25-27* is/are pending in the application.

Of the above, claim(s) *1, 4, 5, 7, 8, 19, 20, 22, 25, and 26* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *12, 23, and 27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 4, 5, and 7, drawn to nucleic acids from influenza viruses and DNA sequences complementary to theses nucleic acids, classified in class 536, subclass 23.1.

II. Claims 8, 22, 25, and,26, drawn to nucleic acids and polynucleotides of influenza virus, specifically M, PB1, PA, PB2, HA and NA sequences , classified in class 536, subclass 23.1.

III. Claims 12, 23, and, 27, drawn to a vaccine comprising a reassortant influenza virus, cold-adapted with wild type NA and HA proteins, classified in class 424, subclass 209.1.

IV. Claims 19 and 20, drawn to methods for the prevention and treatment of influenza virus infection, classified in class 424, subclass 93.3.

2. The inventions are distinct, each from the other because of the following reasons: Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions I and II are drawn to different nucleic acid sequences derived

from influenza virus strains, in particular both inventions include variant sequences of the PB2 gene.

3. Inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case Invention III is drawn to a vaccine for influenza A virus and Invention IV is drawn to a method for the treatment on an influenza A virus infection. Treatment and prevention of an influenza A infection need not be performed with the product of Invention III and prevention of said infection is possible with a multiple of unique vaccines such as subunit vaccines or inactivated vaccines .

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classifications, restriction for examination as indicated is proper.

During a telephone conversation with Ms. Antionette F. Konski on February 7, 1997 a provisional election was made with traverse to prosecute the invention of Group III, claims 12, 23, and 27. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1, 4, 5, 7, 8, 19, 20, 22, 25, and 26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

4. Claims 12, 23 and 27 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "comprising the nucleic acid sequence of claim 25". There is insufficient antecedent basis for this limitation in the claim. The claim language of this dependent claim must be written so as not to refer to material not specifically recited in the independent claim. Applicant should amend the claim so as to clarify the issue. This can be accomplished by incorporation of language of the non-amended claims. For the sake of compact prosecution, the claim has been analyzed as reciting "comprising the nucleic acid sequence of claim 12" in further actions.

5. Claim 12 is vague and indefinite in the recitation "the polynucleotides being operatively linked to each other " as it is not clear what linkage is implied. The sequences could be physically ligated in order to function as polycistronic units or alternatively be so assembled in proximity to one another as found in the viral nucleocapsid structure. Claim 12 should be amended to obviate this rejection. Claim 27 is vague and indefinite in the recitation "a reassortant virus comprising...." ; the actual virus should be stated, in this case influenza A, as there are numerous reassortant viruses that might be implied, many with an RNA genome capable of reassorting; rotavirus for example. Defining the virus as Influenza A would obviate this rejection. Claim 27 objected to because of the following informalities: reassortant is spelled ressortant, this is assumed to be a typographical error. Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C.§ 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. Applicant's claimed invention is directed to mutant, cold-adapted, Influenza A vaccine composed of HA and NA surface proteins from selected wild type influenza A viruses and the internal proteins encoded by specific polynucleotides producing the cold-adaptation phenotype. In Applicant's claimed invention the production of this unique virus (i.e. one that would not be found in natural and/or epidemic or endemic strains) is via the use of the specific claimed polypeptides. However, Applicant has not set forth a method for to allow one skilled in the art to assemble the relevant components i.e the polynucleotides of the claimed invention, in order to produce a viable virus. It is well known in the art that transfection of cDNA or genomic RNA from negative stranded viruses into host cells will not produce a viable virus. The mere recitation of the polynucleotides that have sequences that confer temperature-sensitivity, cold-adaptation, wild type surface epitopes, or any unique quality hardly insures or even allows the ultimate goal which is the assembly of a viable virus particle. In order to produce a live-virus vaccine one skilled in the art must have the ability to reproducibly incorporate the mutant determinants into said viable virus. Transfection of the claimed polynucleotides into host cells

presumably would be unable to produce the reassortant virus of the claimed invention; therefore it must be made clear within the claimed invention that the polynucleotides must be in the viral genome format i.e. negative sense and therefore complementary to the coding sequences of the claimed invention. To assemble these polynucleotides (the negative stranded variants) they must first be completed with influenza nucleoproteins prior to transfection. It is also known in the art that the assembly of the nucleoprotein into virus particles requires a helper virus as a receptacle for the inserted polynucleotides; and therefore Applicant must delineate these conditions and methods of viral engineering within the claimed invention. Applicant is directed to U.S. Patent No. 5,166,057 for the complete description of these influenza viral engineering techniques. In the absence of convincing objective evidence, one skilled in the art would not be able to produce viruses having any insertion or deletion without undue experimentation. Therefore, as the enablement provided by the specification must be commensurate in scope with the claimed invention, applicant should delineate in the claims the proper polynucleotide format to practice the claimed invention and the methodology necessary to establish a reassortant virus from said specific polynucleotides.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 12 and 27 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cox et al (Virology 1988, 167:554-567). The claimed invention is directed to a vaccine comprising a reassortant virus, the virus further comprising polynucleotides coding for the surface proteins of Influenza A virus HA and NA from selected wild type strains. The other proteins of the claimed invention are encoded by polynucleotides for influenza A viral sequences and are encoding the PB1, PA, M, proteins of a cold-adapted influenza virus and a polynucleotide (SEQ ID No. 15) encoding PB2 polymerase protein. Claim 27 is directed to a viral vaccine form a reassortant virus with a further limitation utilizing the nucleic acid sequence of claim 12 i.e SEQ ID No. 15.

The Cox et al reference teaches the identification of sequence changes in the cold-adapted (ca), live attenuated vaccine strain, A/Ann Arbor/6/60 (H2N2). The reassortant viruses that are described derive their hemagglutinin (HA) and neuraminidase (NA) genes from an epidemic variant virus with five or six other genes originating from the ca A/Ann Arbor/6/60 parent virus. They further teach that the ca reassortant viruses have utility in the production of live attenuated influenza vaccines as the five or six internal genes of the ca donor strain are expected to have uniform biological and attenuation properties (Introduction, 1st and 2nd columns). In this reference are presented the entire nucleotide sequences for the six genes of both the wild type and ca A/Ann Arbor/6/60 viruses that are relevant for producing reassortant candidate vaccine viruses. The relevant sequences and proteins that are needed for the vaccine strain production are identified as PB1, PA, M (M1 and M2) and PB2. The sequence SEQ ID No. 15, the PB2

encoding sequence, is presented in Figure 6, page 563 of this reference. The information within this article describing the relevant proteins of the ca quality of influenza A and their sequences formed the basis for rejection of claim 12. The sequence information for SEQ ID No. 15 from the reference along with the viruses designation as a vaccine strain form the basis for the rejection of claim 27.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 12, 23, and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al and Maassab et al (J. Infect. Dis. 1982, 146(6):780-790).

Cox et al teaches an approach for producing live attenuated influenza A vaccines of new epidemic variants by reassortment with a cold-adapted mutant donor strain. The reference describes reassortant viruses that contain HA and NA genes from clinically relevant epidemic strains of the H1N1 and H3N2 variants now endemic in the human population. The reference further teaches that the five or six internal genes are derived from the ca A/Ann Arbor/6/60 parental virus type and the vaccine virus combination is the consequence of mating of this ca virus with the clinical strain (Introduction, 1st paragraph). The reference presents the sequence information of the entire nucleotide sequences for the six genes of both the wt and ca variant in Figures 5-6. The actual sequence differences between the ca and wt viruses are emphasized in

Table 1, page 564 of this reference. The reference further teaches that during clinical studies conducted with investigational ca Influenza A vaccines derived from the ca A/Ann Arbor/6/60 virus no revertants were detected nor was reversion detected in experiments in ferrets (page 564, 2nd paragraph).

Maassab et al teaches that in experiments with the ca A/Ann Arbor/6/60 (H2N2) in ferrets cold recombinants with six genes derived from the ca "master strain" and the two surface proteins from the wt parent strain were attenuated and genetically stable (abstract). The reference further teaches the intranasal inoculation of the vaccine strain using varying doses of the appropriate clone of the ca recombinant strain in a sterile broth carrier. The ca vaccine reassortant was seen to be unable to replicate in the test animal lungs and grew to lower titers in the nasal turbinates in contrast to the wild type virus (Table 1, page 782).

Based upon the above art it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce an live Influenza A vaccine using a cold-adapted "master" or parental strain and to incorporate its ca qualities into a clinically relevant strain by a mating and reassorting methodology. Based upon the sequence data for the internal viral proteins presented in the Cox et al art the relevant mutations that are responsible for the ca phenotype would be immediately obvious. The initial master strain could be created by the incorporation/rescue of these sequences into a helper virus with selection to create the ca master strain of the type described within the claimed invention. Based upon the data and methods presented in the above art one of ordinary skill in the art would be motivated to incorporate the

virus into a pharmaceutically acceptable carrier, sterile broth, for use in intranasal inoculation in both test animals and humans.

All the claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Gottlieb whose telephone number is (703) 305-4504. The examiner can normally be reached on Monday-Friday from 8:30 AM-5:00 PM, (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine M. Nucker, can be reached on (703) 308-4028. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAM
GROUP 180

Paul Gottlieb

Examiner

Art Unit 1813

February 24, 1997